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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,142	KYRKANIDES, STEPHANOS	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43,72-75,83-91 and 133-141* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43,72-75,83-91 and 133-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

10-0

DETAILED ACTION

Applicant's response to the First Action was filed March 7, 2005. Claims 44-71, 76-82, 92-132 have been withdrawn from consideration. Claims 133-141 are newly added. Claims 1-43, 72-75, 83-91, and 133-141 are under consideration.

Claims 1-43, 72-75, 83-91, and 133-141, drawn to a composition comprising a nucleic acid comprising a nucleic acid sequence encoding HEX-α and HEX-β and to a method of making a composition comprising a nucleic acid comprising a nucleic acid sequence encoding HEX-α and HEX-β are under consideration.

Withdrawn Rejections

35 U.S.C. § 102

Applicant's arguments, see page 25, section VI, filed March 7, 2005, with respect to claims 1-4 have been fully considered and are persuasive. The rejection of claims 1-4 has been withdrawn.

35 U.S.C. § 103

Applicant's arguments, see page 25-31, section VII, filed March 7, 2005, with respect to claims 1-41, 72-75, 83-91 have been fully considered and are persuasive. The rejection of claims 1-41, 72-75, 83-91 has been withdrawn.

New and Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-43, 84-91, and 133-141 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. According to the American Heritage online Dictionary, "composition" is defined as: "The combining of distinct parts or elements to form a whole." "Composition" can be read broadly to encompass humans. As such, the claims can be read as "a human comprising a nucleic acid wherein the nucleic acid comprises a sequence encoding a HEX-α and a sequence encoding a HEX-β." Claiming a human is non-statutory matter. This rejection can be obviated by stating, "the composition comprising an isolated nucleic acid..."

Response to Arguments

Applicant's arguments (filed March 7, 2005) with respect to claims 1-4, 72 (rejected in the First Office Action, December 7, 2004) have been considered but are moot in view of the new ground(s) of rejection.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-43, 72-75, 83-86 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-43, 72-75, 83-86 of copending Application No. 10/978,927. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-43, 72-75, 83-91, and 133-141 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1) a tricistronic construct comprising a nucleic acid sequence of SEQ ID NO.3 (encoding human β-hexosaminidase-b h(Hex-b)), a nucleotide sequence of SEQ ID NO. 5 (IRES), a nucleic acid sequence of SEQ ID NO. 1 (encoding hHex-a), a nucleic acid sequence of SEQ ID NO. 5 (IRES), and a lacZ, operably linked to CMV, rat nuclear enolase specific promoter (SEQ ID NO. 69) or a rat pro-collagen 1 A1 promoter (SEQ ID NO. 70 and 71), wherein the construct is inserted into a non-viral mammalian expression vector system;

2) a tricistronic construct comprising a nucleic acid sequence of SEQ ID NO.3 (encoding human β-hexosaminidase-b h(Hex-b)), a nucleotide sequence of SEQ ID NO. 5 (IRES), a nucleic acid sequence of SEQ ID NO. 1 (encoding hHex-a), a nucleic acid sequence of SEQ ID NO. 5 (IRES), and a lacZ, operably linked to CMV, rat nuclear enolase specific promoter (SEQ ID NO. 69) or a rat pro-collagen 1 A1 promoter (SEQ ID NO. 70 and 71), wherein the construct is inserted into a FIV or HIV vector system;

3) TSD ^{hexXAT} construct which comprises: a nucleic acid sequence comprising a transcription STOP site flanked by mammalian recombinase sites, a nucleic acid sequence SEQ ID NO.3 (encoding human β-hexosaminidase-b h(Hex-b)), a nucleotide sequence of SEQ ID NO. 5 (IRES), a nucleic acid sequence of SEQ ID NO. 1 (encoding hHex-a), and a poly A tail, operably linked to CMV; and

4) a method of making the above constructs

does not reasonably provide enablement for

any composition comprising a nucleic acid wherein the nucleic acid comprises any sequence encoding any HEX-α and any sequence encoding any HEX-β.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is to a composition comprising a nucleic acid wherein the nucleic acid comprises a sequence encoding a HEX-α and a sequence encoding a HEX-β and to a method of making a composition comprising a nucleic acid wherein the

nucleic acid comprises a sequence encoding a HEX-α and a sequence encoding a HEX-β. The claims broadly encompass a nucleic acid comprising any integrated ribosomal entry site (IRES), any inducible promoter, any functional HEXB, HEXA, and HEXS gene product, any recombinase site, any vector, any cell specific promoter. The claims, when read in view of the specification, have use in delivering HEX-α and HEX-β in order to ameliorate lysosomal disorders such as Tay-Sachs and Sandoffs disease.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claimed invention broadly encompasses the use of any IRES. The specification teaches the HexlacZ vector (specification, page 82 and figure 1) is a tricistronic construct comprising human β-hexosaminidases (hHexA and hHexB) and lacZ; the TSD ^{hexXAT} construct comprising CMV-loxP-STOP-loxP-HexB-IRES-HexA-pA, which was used in human primary fibroblasts of a Tay-Sachs disease patient (specification, page 84, lines 1-4); FIV(HEX), a FIV vector comprising bicistronic HexB-IRES-HexA (specification, page 87); HIV(HEX), a HIV vector comprising bicistronic HexB-IRES-HexA (specification, page 88); a NSE-Hex construct comprising tricistronic HexB-IRES-HexA-IRES-lacZ operably linked to a rat neuro-specific enolase promoter (SEQ ID NO. 69) (specification, pages 124-125) and; a COLL1-Hex construct comprising tricistronic HexB-IRES-HexA-IRES-lacZ operably linked to a rat pro-collagen 1 A1 promoter (SEQ ID NOs. 70 and 71) (specification, pages 149-150). However, at the time of filing, the art teaches that different IRESes have different abilities to initiate translation. LaPorte et al. (2000, Journal of Virology, 74: 10827-10833) teach that nucleotide differences between IRESes can alter the activity of an IRES. LaPorte et al. teach that a great heterogeneity was observed in translation efficiencies, varying from 3.4 to 93.6% relative to the original reporter vector, pIRF (LaPorte, et al., page 10830, 2nd col., 1st parag., lines 3-5, see also Figure 4). LaPorte et al. teach that the IRES, Q7, was the most efficient, but on the whole, the activity was independent of the number of additional mutations detected (LaPorte, et al., page 10830, 2nd col., 1st parag., lines 5-7). In light of the teachings of LaPorte et al., an artisan cannot predict what mutations will affect the IRES's ability to initiate translation. As such, LaPorte et al. teach in some

cases, wherein the expression driven by some IRESes are so low, an artisan cannot predict, with regards to the instant invention, that using a low translating IRES would be enough to make HEXA and HEXB such that HEXA and HEXB treats a disease. The polycistronic constructs of the claimed invention needs to be held to the standard that it has an effect on a disorder as these are constructs that are used in gene therapy. The specification, at the time of filing, does not teach an artisan how to select any IRES such that it drives production of enough HexB, such that enough HexB is able to make HEXA and HEXB complex. This is undue experimentation, as nothing in the art of the specification provides any guidance as to how to make any IRES. Since art teaches this unpredictability and the specification does not teach an artisan how to overcome this unpredictability, the claimed invention is limited to the IRES taught in the specification, SEQ ID NO. 5.

The claimed invention broadly encompasses the use of any nucleic acid, wherein the nucleic acid is comprised of HEX-α and HEX-β, wherein the nucleic acids encoding HEX-α and HEX-β are put under the control of an IRES. The issue at hand is whether or not an IRES can be used to drive appropriate amounts of HEX-β in a cell to treat a HEX-related disease. The specification, at the time of filing teaches that an expression vector, pHEXlacZ, was comprised of, in 5' to 3' order, a CMV promoter, the nucleic acid sequence encoding human HEXB, an IRES, the nucleic acid sequence encoding human HEXA, an IRES, and a nucleic acid sequence encoding β-galactosidase (Figure 1). FIV(Hex), the lentiviral vector, was comprised of, in 5' to 3' order, a CMV promoter, the nucleic acid sequence encoding human HEXB, an IRES, the nucleic acid sequence

encoding human HEXA, an IRES, and a nucleic acid sequence encoding β-galactosidase (Figure 4). The specification, teaches that HexB is necessary in the synthesis of both HEXA and HEXB, that HexB ORF was cloned first in the transgene (specification, page 83, lines 1-2). At the time of filing, the art supports the teachings of the specification and teaches that use of an IRES to drive appropriate amounts of protein was significantly lower than protein expression driven from a cap-dependent gene. Mizuguchi et al. (2000, Molecular Therapy, 1: 376-382) teach that IRES-dependent gene expression was consistently lower than gene expression driven by the 5' cap. Mizuguchi et al. teach that this was consistent for the different types of reporter genes used and for the different cell lines which were transfected with the construct (Mizuguchi et al., page 377, 2nd col., 1st 2 parag. under "Comparison of First and Second Gene Expression with IRES in Vitro and in Vivo"). While the specification and the art teach that less gene product is made using an IRES, the specification does not teach an artisan that the lower amount of HexB, driven by the IRES, is enough to correct deficiencies in vitro and in vivo. The polycistronic constructs of the claimed invention needs to be held to the standard that it treats a disorder as these are constructs that are used in gene therapy. As such, because an artisan cannot predict that enough HexB would be produced if driven by an IRES and the art and the specification do not overcome the issues addressed in the art (e.g. that enough HexB, driven by an IRES, is produced to make HEXA and HEXB, or that there is way of making an IRES such that it produces protein comparable to levels produced by a 5' cap), that the claimed invention is not enabled for the full breadth of a composition

comprising any nucleic acid wherein the nucleic acid sequences encoding HEX-β can be put under the control of an IRES for translation. Therefore, the claimed invention is limited to the order of: 5' HexB-IRES-HexA-IRES-lacZ.

In addition to the art teaching that a nucleic acid sequence encoding a gene of interest put under control of an IRES for translation is less robust, as compared to a nucleic acid sequence encoding a gene of interest put under control of a 5' cap, the art also teaches that composition and arrangement of genes can define the strength of IRES-driven translation. Hennecke et al. (2001, Nucleic Acids Research, 29 : 3327-3334) teach that "while cap-dependent translation inititation from bicistronic mRNAs remains comparable to monocistronic expression, internal initiation mediated by these viral IRESs is often very inefficient. Expression of bicistronic expression vectors containing the hepatitis B virus core antigen (HbcAg) together with various cytokines in the second cistron of bicistronic mRNAs gave rise to very low levels of the tested cytokines. One the other hand, the HbcAg was well expressed when positioned in the second cistron. This suggests that the arrangement of cistrons in a bicistronic setting is crucial for IRES-dependent translation of the second cistron (Hennecke et al., abstract, lines 9-22)." Henneke et al teach that reporter systems for translation were found to be unpredictable from IRES-containing mRNAs. Hennecke et al. took luciferases from firefly (Fluc) and Renilla (Rluc) and determined the translational efficiency of two reading frames from one mRNA (Henneke, et al., page 3329, 2nd col., 1st parag.). Henneke et al. teach that" luciferase values for the first cistron were very similar irrespective of the gene (Fluc or Rluc) and the existence of a downstream IRES-directed

second cistron.... Expression of the second cistron, however, was dependent on the arrangement of the luciferases on the mRNA. While IRES-dependent translation of Fluc was very strong, that of Rluc appeared 30 fold less efficient. Thus, expression of the two luciferases reflects the unexpected observations of bicistronic expression of HbcAg and cytokines (Henneke et al, page 3330, 1st col., 2nd parag to 2nd col., 1st parag., see also Figure 3)." Henneke et al. also teach that sequence alterations in Fluc affect the efficiency of IRES-mediated translation. Henneke et al. generated Fluz, in which 76.1% of the coding nucleotide sequence is altered. Fluz, when put as the first cistron in a bicistronic construct, affected IRES-mediated translation of the second cistron. Henneke et al. teach that nucleotide exchanges can lead to strong negative effects on downstream IRES-mediated translation (Henneke, et al., page 3332, 1st col., 2nd parag. to 2nd col. 1st parag., see also Figure 5). Therefore, Henneke et al. teach that an artisan cannot necessarily predict what order to place cistrons encoding proteins of interest. This means, with regards to the instant invention, one cannot predict whether insertion of Hex-β, the protein of interest, can necessarily be a second cistron, as the art teaches that the second cistron can unpredictably be expressed at lower amounts. Whether or not this expression level has an impact on the treatment of HEX-related diseases needs to be empirically determined. Further, Henneke et al. teach that nucleotide substitutions can affect the translation of the second cistron. This effect is unpredictable. This means, with regards to the instant invention, one cannot predict whether substitution of nucleic acids in a gene of interest (e.g. claim 12: wherein the HEX–β has at least 70%, 75%, 80%, 85%, 90%, or 95% identity to the sequence set forth in SEQ ID NO: 3 and

the HEX–α has at least 70%, 75%, 80%, 85%, 90%, or 95% identity to the sequence set forth in SEQ ID NO. 1) will affect the translation ability of the second cistron. Since art teaches this unpredictability and the specification does not teach an artisan how to overcome this unpredictability, the claimed invention is limited to SEQ ID NO. 4, the nucleotide sequence encoding human HexB.

With regards to the claimed invention broadly encompassing any functional HEXB, HEXA, and HEXS from any species of animal, the art at the time of filing teaches that an artisan cannot predict that overexpression of any protein of interest would produce an animal with an expected phenotype. For example, Hammer, et al. (1990, Cell 63:1099-1112) demonstrated that transgenic mice that overexpressed human HLA-B27 and human β2-microglobulin (hβ2m) did not develop the human disease, spondyloarthropathies, whereas a rat that overexpressed human HLA-B27 and human β2-microglobulin (hβ2m) did exhibit spondyloarthropathies (page 1099, second column, second paragraph). Hammer et al. teach that an artisan cannot predict that protein from one species of animal will have a similar effect in another species of animal. Further, Hammer et al. teach that an artisan cannot predict that a protein will necessarily have an effect in two animals of similar species. With regards to the instant invention, while the specification teaches that human HEX–α and HEX–β were used in mice, an artisan, based on the teaching of Hammer et al., cannot predict that one is enabled for using HEX–α and HEX–β from any species of animal. The specification as filed does not teach a skilled artisan how to overcome this issue of unpredictability. For this reason,

the specification does not enable a skilled artisan to make any vector comprising HEX–α and HEX–β from any species of animal. Therefore, the specification is limited to the use of human HexA and human HexB.

The claims broadly encompass the use of any transposition system. This includes the P element transposon system that is used in Drosophila. However, the art does not teach that the P element system is used in mammals. It would be undue experimentation for an artisan to use the P element transposon system in a mammal because neither the art nor the specification at the time of filing teach how to make and use a mammal comprising a P element transposon system in the method described.

The claims broadly encompass the use of any inducible system. The specification demonstrates the use of a RU486 inducible system in cell culture. RU486 is used to activate transcription of Cre recombinase, which targets loxP sites (specification, page 5, Figure 14 legend; page 6, Figures 16 and 17 legend). While the specification and art enable the use of an inducible system in vitro, the art teaches that use of an inducible system in vivo is unpredictable. In this system, an external source is used to activate or suppress transcription. Common issues regarding inducible systems include delivery and clearance of the inducer. One factor a skilled artisan would need to consider is how long does it take the system to be activated and does the drug reach its target tissue? In the case of the brain, the drug would need to cross the blood-brain-barrier. In addition to activation, inducible systems would need to be turned off. When turning off the gene, one aspect to consider is how long does it take an

organism to recover from induction. Recovery would encompass issues such as how long does it take the inducer to clear the cell and how long does it take the cell to recover from the induction. These issues would have to be determined empirically. In addition to these issues, dosage of the inducer would also need to be determined: how much should be administered and what route should be used for delivery are questions that are dependent on the tissue/organ examined. At the time of filing, the art teaches an in vivo inducible system using RU486. In this system, Wang et al. (1995, PNAS, USA, 91: 8180-8184) teach that cells from a stable fibroblast cell line comprising the RU486 inducible system was injected into rat muscle. Further, Wang et al. teach that administration of RU486 turned on the transgene in the cell line. While Wang et al. teach this system in muscle, they do not teach that the system can be applied to other tissue, like the nervous system of the instant invention. According to the art at the time of filing, very little RU486 can cross the blood-brain barrier (Heikinheimo and Kekkonen, 1993, Ann Med, 25: 71-76, abstract, see lines 16-22). It is unclear if any of the RU486 that does cross the blood-brain barrier is enough to instant the instant invention, such that enough Hex protein is produced to cause a therapeutic effect in Hex-deficient patients. Additionally, if there was not enough RU486 in the brain that could induce the instant invention, the specification does not teach how one would overcome this issue of enablement. While the specification teaches the RU486 system in vitro, the specification does not teach the system in vivo. In order for an artisan to use the system in vivo would be undue experimentation as factors such as delivery of RU486

does not enable an artisan to use the claimed invention in vivo. Further, the specification does not teach an artisan how to overcome this issue.

The claimed invention broadly encompasses any cell-specific promoter obtained from any species of anima. The specification teaches that NSE was obtained from the rat and that COLL1 was obtained from the rat. However, teachings in the art shows that use of any cell-specific promoter from any species of animal is unpredictable. Cowan et al. (2003, Xenotransplantation, 10: 223-231) teach that promoters of three human genes, ICAM-2, hCRPs, and PECAM-1, which are predominantly expressed in vascular endothelium in mice and pigs. When tissue specific expression was measured, it was found that while mice showed a distinct expression profile of the three human genes, the tissue expression profiles of the three human gene promoters were distinctly different in pigs. The authors concluded that "promoter performance in mice and pigs was not equivalent," and that "the weak expression driven by the human ICAM-2 promoter in pigs relative to mice suggests the need for additional regulatory elements to achieve species-specific gene expression in pigs. Cowan et al. teaches that tissue specific promoters, used in different species of animals is unpredictable. The specification does not overcome the unpredictability in the art and teach an artisan how to predictably make a construct comprising any cell-specific promoter from any species of animal without undue experimentation. The experimentation is undue because of the unpredictability in selecting a promoter. An artisan would need to determine empirically if any cell specific promoter obtained from any species of animal is appropriate for one's

application. No guidance was provided as to how one would obtain any cell-specific promoter from any species of animal and express it predictably in any animal. Therefore, the claimed invention is limited to only a rat NSE promoter and a rat COLL1A1promoter.

The specification is enabled for the use of a rat NSE promoter and a rat COLL1A1 promoter. Use of any rat NSE promoter and any rat COLLA1 promoter encompasses promoters of any size. While the specification teaches that the rat NSE promoter used in the instant invention is SEQ ID NO: 69 and that the rat COLL1A1 promoter used in the instant invention is SEQ ID NO. 70 or SEQ ID NO. 71, the specification does not teach how to obtain any rat NSE promoter and any COLL1A1 promoter of any size. The art at the time of filing teaches that the identification of any promoter was unpredictable. Goswami et al. (2003, Journal of Molecular Evolution, 57:44-51) teach some of the analyses used to characterize a promoter. Goswami et al. show by 5' deletion analysis that BD2, a greater 5' deletion of the TGF-β5 promoter than BD3, has more activity than BD3, suggesting that the 5' deletion in BD2 uncovered a negative regulator in the promoter (page 46, column 2, first paragraph, lines 3-7). Goswami et al. also show that while there is this difference in promoter activity between the two constructs transfected in XTC cells (*Xenopus* tadpole cell line), there is no difference in the activity of the promoters when transfected in A6 cells (*Xenopus* adult kidney fibroblast cell line). This result suggests that there is a difference in the transcriptional factors between the cell types (page 46, column 2, first paragraph, lines 7-10). Goswami et al. also show that there is a difference in promoter regulation,

depending what animal species that promoter is from and into which cells the reporter construct is transfected. TGF-β5, which is found in rats and frogs, was found to be regulated differently. *Xenopus* TGFβ-5 transfected into *Xenopus* cells had activity; it had little to no activity when transfected into mammalian cells (page 47, column 2, section headed "Basal Promoter Activites of TGFβ1 and TGF-β5 Promoter in Mammalian Cell Lines", see also Figures 3 and 4). As illustrated by Goswami, selecting a regulatory region of a gene as a promoter is not intuitive and requires extensive characterization. A good deal of the unpredictability in isolating any promoter stems from the fact that it is not know what transcription factors bind to a promoter and regulate it. With respect to the instant invention, an artisan cannot necessarily delete regions of SEQ ID NO. 69, 70, 71 and expect it to function like SEQ ID NO. 69, 70, 71. Further, an artisan cannot necessarily obtain more of the promoter sequence from genomic DNA and expect it to have the same activity as SEQ ID NO. 69, 70, 71. Obtaining any promoter is undue experimentation as each one obtained would need to be determined empirically for activity. One skilled in the art cannot define a regulatory region of a gene as a promoter and expect that another skilled in the art would select the same sequence without guidance. Therefore, the NSE and COLL1A1 promoters are limited to SEQ ID NOs 69, 70, 71.

The claimed invention encompasses any DNA vector as a vehicle to deliver the therapeutic transgene. This includes viral and non-viral DNA vectors. The art teaches that viral and non-viral vectors are unpredictable or have limited capabilities because

delivery of a DNA vector is unpredictable or limited. The art teaches several ways that non-viral DNA eukaryotic vectors could be introduced into cells. For example, Wolff et al. teach that some methods of directly introducing non-viral DNA vectors into the animal include non-viral DNA encapsulated in liposomes, non-viral DNA entrapped in proteoliposomes containing viral envelope receptor proteins, calcium phosphate-coprecipitated DNA, and DNA coupled to polylysine-glycoprotein carrier complex (Wolff, et al., 1990, Science, 247: 1465-1468; page 1465, 1st col., 1st parag., lines 11-18). Wolff et al. teach that non-viral DNA vectors can also be directly injected into muscle. However, the non-viral DNA vector, depending on its route of administration, only localizes to certain tissues or organs. As a result, the vector is not readily distributed throughout the body. For example, Wolff et al. show that the non-viral DNA is localized to the muscle at the site of injection (Wolff, et al., page 1465, 3rd col., 2nd parag.) Nicolau et al. demonstrated that non-viral DNA suspended in liposomes and injected intravenously are localized to the liver and the spleen (Nicolau, et al., 1983, PNAS, USA, 80: 1068-1072; page 1068, 1st col., 1st parag.). With regards to the instant invention, while one way may be direct injection to the brain, Wolff et al.'s teaching demonstrates this would only be effective for the region that received the injection. This means that one would need to inject the brain in multiple sites in order to treat all neurons affected by Hex deficiency. While one may try the method of Nicolau et al., a good part of the vector would end up in the liver and spleen. While one may argue that cross-correcting (i.e. be released extracellularly and be absorbed by paracrine pathways by other cells whereby they contribute to β-hexosaminidase activity, see

specification, page 3, lines 9-11), the specification teaches that one problem with cross-correcting is that the protein cannot cross the blood-brain-barrier (specification, page 1, lines 25-30). Another problem associated with using non-viral DNA vectors is that they suffer from inefficient gene transfer. Abdallah et al. (1995, Biol. Cell., 85: 1-7) teach that one of the major hurdles in using non-viral DNA *in vivo* is successfully having the vector enter the nucleus (Abdallah, et al., page 2, 1st col., 2nd parag.). In addition to this, expression from these non-viral vectors is transient (Somia and Verma, 2000, Nature Reviews, 1:91-99; page 91, 1st col., 2nd parag., lines 2-8)). While it may be that the instant invention is to expression HEX in the liver or muscle, and the time of expression required to use the instant invention transient, the specification does not teach that these are the embodiments which are used to practice the invention. Rather, a skilled artisan would need to determine the duration of gene expression needed to treat a HEX patient, determine whether or not the means of introducing a non-viral DNA expression vector is sufficient for duration of the treatment and determine whether the transgene is expressed at effective levels. To determine these parameters require undue experimentation. In addition to these parameters, a skilled artisan needs to also consider the fact that gene transfer from non-viral vectors is unpredictable. In other words, it may not even be a salient system to use for gene expression. For reasons of unpredictability and undue experimentation, the specification has not enabled a skilled artisan to reliably obtain mice injected with a non-viral transgene construct.

With regards using any viral vector as a vehicle to deliver HexA or HexB, the art teaches that viral vectors as a vehicle is unpredictable. These issues of unpredictability

include immune responses to the transgene product, the dose of virus administered, the promoter chosen to drive expression of the recombinant gene, the innate immune mechanisms and direct cytotoxcity cause by expression of viral genes (e.g. see Somia and Verma, page 92, Box 1). With regards to an adenoviral vector, the vector remains episomal, and expresses a transgene transiently. For these reasons, the use of a viral vector is determined empirically. While the specification teaches the use of FIV and HIV vectors in mice (e.g. specification, page 87), the specification does not teach how to use other viral vectors, such as adenoviral vectors. The specification does not teach how to overcome the issues associated with adenoviral vectors (such as host immune response) or whether short-term expression of Hex is enough to treat Hex-deficient patients. However, the specification as filed does not provide sufficient guidance, working examples, and evidence as to how an artisan of skill would have made and used the claimed invention commensurate with the scope of the claims without undue experimentation.

Claims 1-43, 72-75, 83-91, and 133-141 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification and the art provides adequate written description for the isolated nucleic acid sequences designated by SEQ ID NOs: 1, 3, 5, 69, 70, 71, the specification fails to adequately describe other nucleic acid sequences which hybridize to these sequences that do not encode these proteins. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional

in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed invention broadly encompasses a nucleic acid comprising any integrated ribosomal entry site (IRES), any inducible promoter, any functional HEXB, HEXA, and HEXS gene product, any recombinase site, any vector, any cell specific promoter. However, as described above in the enablement section, above, the claims are not enabled for the full breadth of the claims. While it may be that the claimed invention could encompass other embodiments such as a Hex-β having at least 70% identity to the sequence set forth in SEQ ID NO. 3, nothing in the specification teaches an artisan what part of 70% of SEQ ID NO. 3 would need to remain intact, in order for the encoded protein to function. Similarly, the claims encompass a "conservative change (e.g. see claim 13)" or sequences encoding HEX-β, wherein the sequence is obtained under "stringent conditions (e.g. see claim 15)." However, no guidance was provided as to where the changes could occur and what amino acids could be substituted and result in a "functional" protein or a "functional" Hex complex (e.g. claim 26). In other words, while the specification teaches in great detail the many parameters one can change in hybridization conditions to obtain a nucleic acid sequence by altering the temperature, salt concentrations, time of incubation, length of nucleic acid and composition of the

nucleic acid composition, the specification fails to describe the relevant identifying characteristics of all the nucleic acid sequences which hybridize and function as HEX-β. The skilled artisan cannot envision all the possible variant nucleic acid sequences which would hybridize and function as HEX-β, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only human Hex-a (SEQ ID NO. 1), human Hex-B (SEQ ID NO. 3), IRES (SEQ ID NO.5), the rat nuclear enolase specific promoter (SEQ ID NO. 69), and the rat COLL1A1 promoter (SEQ ID NO. 70 and SEQ ID NO. 71), meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant's arguments (filed March 7, 2005) with respect to claims 1-13, 15-18, 20-22, 24-31, 39-43, 72-75, 84-88, 90 (in the rejection made in the First Office Action, filed December 7, 2004) have been considered but are moot in view of the new ground(s) of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 recites the limitation "the second IRES sequence is located 3' to the other parts" in claim 10. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

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